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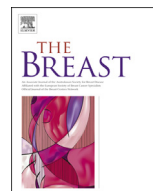
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Original article

Reduction mammoplasty in patients with history of breast cancer: The incidence of occult cancer and high-risk lesions



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ABSTRACT

Introduction: Contralateral reduction mammoplasty is regularly included in the treatment of breast cancer patients. We analyzed the incidence of occult breast cancer and high-risk lesions in reduction mammoplasty specimens of women with previous breast cancer. We also analyzed if timing of reduction mammoplasty in relation to oncological treatment influenced the incidence of abnormal findings, and compared if patients with abnormal contralateral histopathology differed from the study population in terms of demographics.

Materials and methods: The study consisted of 329 breast cancer patients, who underwent symmetrizing reduction mammoplasty between 1/2007 and 12/2011. The data was retrospectively analyzed for demographics, operative and histopathology reports, oncological treatment, and postoperative follow-up. **Results:** Reduction mammoplasty specimens revealed abnormal findings in 68 (21.5%) patients. High-risk lesions (ADH, ALH, and LCIS) were revealed in 37 (11.7%), and cancer in six (1.9%) patients. Abnormal histopathology correlated with higher age ($p = 0.0053$), heavier specimen ($p = 0.0491$), and with no previous breast surgery ($p < 0.001$). Abnormal histopathological findings were more frequent in patients with reduction mammoplasty performed prior to oncological treatment ($p < 0.001$), and in patients with immediate reconstruction ($p = 0.0064$).

Conclusion: The incidences of malignant and high-risk lesions are doubled compared to patients without prior breast cancer. Patients with abnormal histopathology cannot be preoperatively identified based on demographics. If reduction mammoplasty is performed before oncological treatment, the incidence of abnormal findings is higher. In the light of our results, contralateral reduction mammoplasty with histopathological evaluation in breast cancer patients offers a sophisticated tool to catch those patients whose contralateral breast needs increased attention.

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1. Introduction

Contralateral symmetrizing reduction mammoplasty is regularly included in the operative plan of breast cancer patients. It is performed simultaneously with mastectomy or cancer resection, during immediate or delayed breast reconstruction, or later in the process. Patients with breast cancer history are at some risk of developing a contralateral breast cancer. Although modern imaging

and oncological treatment have lowered the incidence of contralateral cancer to 0.25%–0.75% annually [1–3], it comes as no surprise that occult breast cancer as well as high-risk lesions may be revealed in reduction mammoplasty specimens. The incidence of occult cancer in reduction mammoplasties aimed at symmetrization varies from 0.94% to 5.45% [4–14]. However, the differences in the definition of clinically relevant breast histopathology, as well as inclusion of lobular carcinoma in situ (LCIS), lead to discrepancies. When only invasive cancer and ductal carcinoma in situ (DCIS) are taken into account, the incidence of occult breast cancer ranges from 0.94% to 3.64% [4–14] in breast cancer patients.

Our aim was to report the incidence of occult breast cancer and high-risk lesions in reduction mammoplasty specimens in patients with a history of breast cancer from a high-volume center. We also

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analyzed if timing of reduction mammoplasty in relation to oncological treatment influenced the incidence of abnormal findings in reduction mammoplasty specimens, and compared if patients with abnormal histopathology differed from the study population in terms of demographics.

2. Material and methods

The study population consisted of 329 breast cancer patients, who underwent symmetrizing reduction mammoplasty in the Department of Plastic and Reconstructive Surgery, Helsinki University Hospital, between January 2007 and December 2011 including postoperative follow-up until the end of December 2016. The data was retrieved from patient records and retrospectively analyzed for demographics, operative and histopathology reports, oncological treatment, and postoperative follow-up.

Experienced pathologists analyzed histopathology of the specimens. After fixing with formalin, the specimens were weighed and examined macroscopically for masses or for areas of increased density. Specimens were cut into one cm slices, and samples for tissue blocks were taken from macroscopically suspicious areas and evaluated histopathologically. The number of tissue blocks varied between three and 22, six being the most usual number.

Histopathological findings in reduction mammoplasty specimens were categorized based on consensus statement outlined by the Cancer Committee of the American Pathologists [15]. Abnormal histopathological findings in our study included proliferative breast lesions without atypia, atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), and invasive cancer. Low-risk lesions included intraductal papilloma and sclerosing adenosis. High-risk lesions included ADH, ALH, and LCIS. Invasive cancer and DCIS were categorized as cancer findings due to their similar clinical management. All other histopathological findings were defined as normal breast tissue. For statistical purposes, patients with abnormal histopathology were categorized to subgroups based on the most severe finding, e.g. a patient with both low-risk and high-risk lesions was included in the high-risk group. In 12 (3.6%) patients, no sample was taken for histopathological analysis. The percentages of abnormal findings were calculated from the number of samples available ($n = 317$).

Primary breast cancers were recorded. For statistical purposes smaller subgroups, such as papillar, micropapillar, mucinous, tubular and tubulolobular cancer, were connected to the ductal cancer group by an experienced pathologist.

Mean values (\pm SD) were reported for continuous variables. Pearson's chi-squared test was applied in bivariate analyses between categorical variables. Mann-Whitney U test was applied for testing differences in medians between two groups, when variables did not follow normal distribution. Two-sample t -test and analysis of variance were used when patient age was compared between

patient groups. P-values less than 0.05 were considered statistically significant.

3. Results

A total of 329 patients with a mean age of 56.3 ± 8.2 years underwent reduction mammoplasty. Histopathological evaluation of reduction mammoplasty specimens revealed abnormal findings in 68 (21.5%) patients and normal breast tissue in 249 (78.5%) patients. In 12 (3.6%) patients, with a mean age of 53.5 ± 6.5 years, no sample was obtained for histopathological analysis. The mean age (SD), smoking history, previous breast surgery, and the mean weight (g) of the specimen of the patients with normal and abnormal histopathology are listed in Table 1. There was a significant difference in age ($p = 0.0053$), specimen weights ($p = 0.0491$) and incidence of previous breast surgery ($p < 0.001$) between patients with abnormal and normal histopathology so that abnormal histopathology correlated with higher age, heavier specimen, and with no previous breast surgery. The incidences of different forms of primary cancer in patients undergoing contralateral reduction mammoplasty and histopathological evaluation are listed in Table 2.

3.1. Histopathology

Evaluation of reduction mammoplasty specimens revealed abnormal histopathological findings in 68 (21.5%) patients with a mean age of 58.9 ± 8.5 years. The incidences of abnormal histopathological findings in reduction mammoplasty specimens are presented in Table 3. Two simultaneous abnormal findings were revealed in 12 patients and three simultaneous abnormal findings in one patient.

In total, low-risk lesions (sclerosing adenosis, intraductal papilloma) were revealed in 35 (11.0%) patients, high-risk lesions (ADH, ALH, and LCIS) in 37 (11.7%) patients and cancer in six (1.9%) patients. The incidence of abnormal histopathological findings by age is presented in Tables 4a and 4b. In age comparisons, for statistical purposes, patients with abnormal histopathology were categorized to subgroups based on the most severe finding, e.g. patient with both low-risk and high-risk lesions was included in the high-risk group. Abnormal histopathological findings in total ($p = 0.0088$) were more frequent with increasing age. Statistical analysis for smaller subgroups was not reliable due to low number of findings per different age groups.

3.2. The timing of reduction mammoplasty

Reduction mammoplasty was performed before oncological treatment in 77 (23.4%) patients and after oncological treatment in 252 (76.6%) patients. Abnormal histopathological findings were statistically more frequent ($p < 0.001$) in patients with reduction mammoplasty performed before oncological treatment (42.1%)

Table 1
Demographic characteristics of the patients.

Demographic data	Normal histopathology $n = 249$	Abnormal histopathology $n = 68$
Mean age ^a	55.8 ± 8.1	58.9 ± 8.5
Positive smoking history	19 (7.6%)	2 (2.9%)
Previous breast surgery ^a		
• No	26 (56.5%)	20 (43.5%)
• Yes	223 (82.3%)	48 (17.7%)
Mean weight (g) of the specimens ^a	342.8 ± 256.6	398.2 ± 254.9

Plus-minus values are means \pm SD.

^a There is a statistical difference in age ($p = 0.0053$), specimen weights ($p = 0.0491$) and incidence of previous breast surgery ($p < 0.001$) between patients with abnormal and normal histopathology.

Table 2

The incidences of different forms of primary cancer in patients undergoing contralateral reduction mammoplasty and histopathological evaluation.

Primary cancer	Normal histopathology n = 249	Abnormal histopathology n = 68
DCIS	21 (8.4%)	12 (17.6%)
IDC	157 (63.1%)	45 (66.2%)
ILC	45 (18.1%)	8 (11.8%)
IDC and ILC	10 (4.0%)	2 (2.9%)
Other	5 (2.0%)	1 (1.5%)
Unknown	11 (4.4%)	0 (0.0%)

DCIS: Ductal carcinoma in situ, IDC: Invasive ductal cancer, ILC: Invasive lobular cancer, IDC and ILC: Both Invasive ductal and lobular cancers, Other: Malign Phylloid Tumor, Both Paget disease and DCIS, or Both Paget disease and IDC.

Table 3

Abnormal histopathological diagnosis in reduction mammoplasty specimens.^a

Diagnosis	Number of patients	%
Sclerosing adenosis	24	7.6%
Intraductal papilloma	12	3.8%
Atypical ductal hyperplasia	30	9.5%
Atypical lobular hyperplasia	5	1.6%
Lobular carcinoma in situ	4	1.3%
Ductal carcinoma in situ	5	1.6%
Ductal cancer	1	0.3%
Lobular cancer	1	0.3%

^a Two simultaneous abnormal findings were revealed in 12 patients and three simultaneous abnormal findings in one patient. One patient had both ductal cancer and ductal carcinoma in situ finding at the same time in reduction mammoplasty specimen.

compared to 14.9% if surgery was performed after oncological treatment. The patients receiving neoadjuvant therapy (n = 5) were assigned to the latter group.

3.3. Breast reconstruction

Breast reconstruction was performed in 159 (48.3%) patients, of which immediate reconstruction in 33 (20.8%) and delayed reconstruction in 126 (79.2%) patients. The patients undergoing immediate reconstruction after neoadjuvant therapy (n = 2) were assigned to the first group. In breast reconstruction patients, contralateral reduction mammoplasty revealed abnormal histopathological findings in 31 (20.3%) patients, and histopathology was normal in 122 (79.7%) patients. There was a statistical difference (p = 0.0064) in patients with abnormal histopathology between immediate and delayed reconstruction so that

histopathology was abnormal in 15.7% with delayed reconstruction versus 37.5% with immediate reconstruction.

3.4. Primary cancer

To analyze if primary cancer type affected the incidence of abnormal histopathological findings in reduction mammoplasty specimens was not possible due to the small number per primary cancer type.

3.5. Postoperative follow-up

Postoperative follow-up until the end of December 2016 was included. The mean follow-up time was 7.4 ± 1.4 years. During this time, three patients were diagnosed with a new cancer in the reduced breast. Reduction mammoplasty specimens had revealed ADH in one, and mastopathia chronica in one of these patients. In the third case, no sample for histopathological analysis had been taken. The patient with ADH in the specimens was later diagnosed with DCIS. The other two were diagnosed with DCIS and invasive cancer, respectively.

4. Discussion

We detected a considerable number (21.5%) of abnormal histopathological findings in reduction mammoplasty patients with a previous history of breast cancer. Our earlier study with reduction mammoplasty patients without a history of breast cancer showed the incidences of occult breast cancer and high-risk lesions of 1.2% and 5.5%, respectively [16]. When compared to the present study (the incidence of cancer 1.9%, the incidence of high-risk lesions 11.7%), the incidences doubled in patients with a history of breast cancer. Similarly, others [4–13] have noticed that history of breast cancer increases the incidence of abnormal findings in reduction mammoplasty specimens. A point worth noticing in breast cancer patients is that the incidence of abnormal findings in contralateral reduction mammoplasty is calculated per one breast compared to e.g. macromastia patients with the incidence calculated per both breasts. Still, the incidence of abnormal findings often multiplies in breast cancer patients. Thus, this supports the importance of histopathological evaluation of reduction mammoplasty specimens.

Benign breast disease is a prominent predictor of future breast cancer risk [15,17–26]. Hartmann et al. [26] showed a 29.0% cumulative incidence of breast cancer at 25 years in women with ADH or ALH, and similarly, King et al. [23] showed a 2.0% annual incidence of breast cancer among women with LCIS and an overall

Table 4a

Abnormal histopathological findings by age groups.

Finding	<40 (n = 10)	40–49 (n = 46)	50–59 (n = 143)	>60 (n = 118)	Total (n = 317)
Normal histopathology	9 (90.0%)	37 (80.4%)	122 (85.3%)	81 (68.6%)	249 (78.5%)
Abnormal histopathology ^a	1 (10.0%)	9 (19.6%)	21 (14.7%)	37 (31.4%)	68 (21.5%)

^a Abnormal histopathological findings (p = 0.0088) were more frequent with increasing age.

Table 4b

Abnormal histopathological findings by age groups.^a

Finding	<40 (n = 10)	40–49 (n = 46)	50–59 (n = 143)	>60 (n = 118)	Total (n = 317)
Normal histopathology	9 (90.0%)	37 (80.4%)	122 (85.3%)	81 (68.6%)	249 (78.5%)
Low-risk lesion	1 (10.0%)	1 (2.2%)	13 (9.1%)	11 (9.3%)	26 (8.2%)
High-risk lesion	0 (0.0%)	7 (15.2%)	7 (4.9%)	22 (18.6%)	36 (11.4%)
Cancer	0 (0.0%)	1 (2.2%)	1 (0.7%)	4 (3.4%)	6 (1.9%)

^a For statistical purposes, patients with abnormal histopathology were categorized to subgroups based on the most severe finding, e.g. patient with both low-risk and high-risk lesions was included in the high-risk group.

cumulative cancer incidence of 26.0% at 15 years. The incidence of high-risk lesions in reduction mammoplasty specimens in patients with a history of breast cancer is higher compared to patients without prior breast cancer. Li et al. [7] showed that the frequency of detecting atypical proliferative lesions in patients with history of breast cancer is significantly higher than in patients without previous breast cancer (12.8% versus 4.3%). Also Ishag et al. [9] and Freedman et al. [12] have demonstrated a higher incidence of high-risk lesions in breast cancer patients compared to patients without history of breast cancer, 7.1% versus 0.97%, and 17.9% versus 3.3%, respectively. As the importance of high-risk lesions for the patients is clear over time, reduction mammoplasty can capture this patient group for future surveillance.

In our study, patients with abnormal histopathology were older, their specimens were heavier, and if previous breast surgery was conducted, the histopathology was more often normal. In our previous study with patients without history of breast cancer [16] we detected similar trend regarding age and specimen weight. Based on these findings it is difficult to define a certain threshold to preoperatively catch patients with abnormal histopathology or to securely say that histopathological examination can be ruled out based on a certain age group. For example, in this study, in age group under 50 years old, there were seven (19.4%) patients with high-risk lesions and one (16.7%) patient with cancer. We do, however, recommend that the heavier specimen of older patients might benefit from more frequent sampling. The majority of the patients with previous breast surgery were operated for breast cancer before contralateral reduction mammoplasty, and received postoperative oncological treatment. This may explain the protective effect of previous breast surgery.

The majority (76.6%) of reduction mammoplasties were performed after oncological treatment. However, abnormal histopathological findings were statistically more frequent in patients with surgery performed before oncological treatment. This may be explained by modern imaging and oncological treatment that lower the incidence of contralateral cancer [1–3]. Also, the use of chemoprevention for risk management has been shown to reduce breast cancer incidence among women with atypical hyperplasia and LCIS at 10 years from 21.3% to 7.5% [25]. Similarly, King et al. [23] showed a reduction in breast cancer incidence at 10 years from 21% to 12% in women with LCIS on chemoprevention compared to women with no chemoprevention. Thus, this puts emphasis on histopathological evaluation of reduction mammoplasty specimens in breast cancer patients with reduction mammoplasty performed before oncological treatment.

In our study, breast reconstruction was performed for 48.3% of the patients. In this patient group, abnormal histopathological findings were statistically more frequent, if reconstruction was performed immediately. As we stated above, oncological treatment seems to play a role in the incidence of abnormal findings in reduction mammoplasty specimens. In our previous study [27], we demonstrated that preoperative imaging does not sufficiently detect high-risk or malignant lesions. Therefore, histopathological evaluation of reduction mammoplasty specimens seems mandatory.

We acknowledge some limitations to our study. Due to its retrospective nature, we could not standardize histopathological sampling. Nevertheless, this study cohort represents common plastic surgery practice.

5. Conclusion

Reduction mammoplasty specimens in breast cancer patients reveal a considerable amount of malignant and high-risk lesions commonly multiplied compared to patients without prior breast

cancer history, and especially frequently if reduction mammoplasty is performed prior to oncological treatment. In the light of our results contralateral reduction mammoplasty followed by histopathological evaluation in breast cancer patients offers a sophisticated tool to catch those patients whose contralateral breast needs increased attention. This works without going into needless s.c. risk-reducing bilateral mastectomies and implant based reconstructions advocated by patients fears for cancer and industry lead insurance policies, increasing in popularity in many countries.

Conflict of interest statement

None.

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Ethical consent

The ethical approval was not required.

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